

## REMARKS

### Claim objections

As a preliminary matter, it is noted that the error in numbering the claims, as pointed out by the Examiner, has been corrected in the claims summary that appears above as part of this response. The status of claims 213 and 214 is now noted as canceled for both. Claims presented in Applicants' previous response as claims 213-218 are now numbered correctly as 215 through 220. The Examiner's attention in this matter is acknowledged with gratitude.

Claims 149, 150, 152, 164, 165, 168, 169, 171-176, 178, 179, 182, 185, 187, 189, 208, 210, 212, and 215-220 are currently pending in the application.

All claims currently in the application stand rejected under 35 USC §103(a) as being unpatentable over Curatolo (US 5,605,889) in view of Urquhart et al., US 4,851,231. The Examiner stated, in pertinent part:

Curatolo et al. teaches a dosage form of azithromycin which can be administered to a mammal. The azithromycin can be in various forms such as a pharmaceutically acceptable salt, anhydrous or hydrous, or as a dihydrate and are formulated from about 25 mg to about 3 grams (col. 4, lines 51-61). Column 2, lines 45-54 teach that the composition can be administered as a tablet or in unit dosage packets "sachet" comprising the azithromycin and a pharmaceutically acceptable carrier. Column 6, lines 62-67 teach the use of binders such as cellulose derivatives. It is taught in column 8, lines 19-27 that the drug could be formulated into a powder for the purposes of making oral suspensions. Column 7, lines 61-64 teach that a coating can be employed. The prior art does not teach the dosage form being delivered to the gastrointestinal tract as claimed. It is also not taught the dosage form comprising a plurality of microparticles.

Urquhart et al. discloses a system for delivering drug in selected environment of use. Column 1, lines 38-41 teaches drugs where administration to the stomach should be avoided, in line 40 is disclosed antibiotics such as erythromycin. Column 5, lines 47-62 describe FIG. 5 as comprising individual tiny reservoirs comprising a core of beneficial agent, surrounded by a wall formed by a release rate material. It is also taught that the reservoirs may contain one or more layers. Column 7, lines 26-51 disclose exemplary materials of which can be used in the release rate controlling material. Column 8, line 5 teaches that erythromycin can be used in the dosage form. Lines 34-47 of column 8 teaches that the amount of drug that can be used is about 10 ng to 25 mg and the diameter of the tiny reservoirs can be about 100 microns to about 2000 microns.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the teachings of Urquhart in the invention of Curatolo et al. to disclose the claimed invention. Urquhart teaches a formulation for the administration of drugs in selected environments where delivery to the stomach should be avoided and Curatolo et al. teaches a dosage form of azithromycin.

The expected result would be a controlled release dosage form of azithromycin wherein the azithromycin is delivered into the gastrointestinal tract of the human. [Office Action, pages 3 and 4]

The rejection is traversed on the basis that (1) the references are not properly combinable and (2) it is based on hindsight.

The references are not properly combinable

It is Applicants' position that Curatolo, which is directed to quick release, in fact teaches away from Urquhart, which is directed to controlled release. One of ordinary skill in the art would simply not find it obvious to combine a reference directed to fast release (Curatolo), with a reference that in essence seeks to do the opposite, i.e., delay the release of a drug. It is well settled law that if references are to be combined, there (1) must be a suggestion to combine them grounded in the prior art and (2) the prior art must provide an expectation of success.

Mere fact that teachings found in prior art could be combined as proposed by patent examiner does not make combination obvious absent some teaching, suggestion, or incentive supporting proposed combination; in present case, examiner failed to identify any such teaching, suggestion, or incentive to support proposed combination of two prior art references (Ex parte Metcalf, BdPatApp&Int (unpub), 5/2/03) . . . Page 1633

Also, see In re Bond, 15 Uspq2d 1566 (Fed. Cir. 1990) in which it was held that the PTO erred in rejecting a claimed invention as an obvious combination of the teachings of two prior art references when the prior art provided no teaching, suggestion, or incentive supporting the combination. See also Smithkline Diagnostics v. Helena Laboratories Corp., 8 USPQ2d 1468, where the court stated that a challenger to the validity of a patent "cannot pick and choose among the individual teachings of assorted prior art references to recreate the claimed invention"; the challenger has the burden to show some teaching or suggestion in the references to support their use in the particular claimed combination. See also In re Mahurkar Patent Litigation, 28 USPQ2d 1801 (N.D. Ill. 1993) where it was stated that decomposing an invention into its constituent elements, finding each element in the prior art, and then claiming it is easy to reassemble these elements into the invention is a forbidden *ex post* analysis.

Applying the law discussed above to the instant rejection, there is clearly no basis for combining Curatolo and Urquhart, particularly in view of the fact that each document teaches away from the other.

Curatolo is not addressed to and does not disclose controlled release dosage forms. Curatolo in fact teaches immediate and/or fast release and, accordingly, teaches away from the instant invention. Curatolo is grounded in the determination that certain dosage forms which release azithromycin quickly for dissolution avoid adverse food effects. Quick release and dissolution are therefore important features for the dosage forms disclosed in Curatolo. See, for example, the following quotation from Curatolo:

The inventors have demonstrated that azithromycin breaks down if exposed to stomach juices which inherently exhibit acid pH. Thus,...it is surprising that rapid disintegration in the GI tract appears to be of importance to the invention. [Curatolo, column 4, lines 30-35]

See also the following quotation:

It is believed that the azithromycin dosage forms of the invention do not exhibit a food effect in large part because they either provide azithromycin ready for dissolution in the GI tract essentially immediately following ingestion (suspensions) or they disintegrate rapidly following ingestion (tablets) and thereby provide azithromycin rapidly for dissolution.

Clearly, a touchstone of Curatolo is fast disintegration and/or fast dissolution to provide azithromycin in the GI tract as soon as possible. There are no embodiments disclosed in Curatolo in which a dosage form is deliberately engineered in order to slow down azithromycin release, as in the instant invention, so that the bulk of azithromycin release occurs distal to the duodenum. Applicants' delayed release dosage forms are engineered to release the bulk of their contained azithromycin after the duodenum. But, delayed release is simply not a factor that makes any sense in the context of the primary reference, i.e., in Curatolo's no- or low- food effect dosage forms. Rather, quick and/or immediate release is an important factor in Curatolo, i.e., clearly the opposite of what the inventors are seeking to achieve in the instant invention. The instant invention is, quite simply, focused on a different problem that employs different considerations than Curatolo. Thus one skilled in the art who was interested in achieving azithromycin controlled release, i.e., delayed release as in the instant invention, would dismiss the Curatolo reference out of hand as irrelevant. Most importantly, one of ordinary skill in

the art would find no reason supporting combining Curatolo and Urquhart since their teachings -- fast release vs. delayed release -- are antithetical to each other.

The Examiner appears to be trying to supply the missing motivation with the secondary reference Urquhart, based on the statement in Urquhart that "Column 1, lines 38-41 teaches drugs where administration to the stomach should be avoided..." coupled with the disclosure in Urquhart of erythromycin. That reasoning is traversed as being clearly based on hindsight. Erythromycin and azithromycin are distinct from each other, are structurally different drugs and have very different properties. For example, erythromycin has a short elimination half life and must be given 3 or 4 times daily for at least 10 days. Azithromycin has a 69 hour half life and can be given once per day for 1, 3, or 5 days. Other significant differences abound between these two different drugs. Indeed, during the prosecution of Curatolo (US 5,605,889), patentees submitted a Rule 132 declaration demonstrating many of those differences. A copy of that declaration, reproduced from Applicants' file copy, is attached hereto as Exhibit A for the convenience of the Examiner. Attention is particularly directed to Paragraph 2, reproduced immediately below:

2. Azithromycin is an azalide antibiotic with chemical, physical, biological and pharmaceutical properties quite different from other antibiotics, including erythromycin. Further, azithromycin is 326 times more stable than erythromycin in solution (Fiese and Steffen, Journal of Antimicrobial Chemotherapy, 1990, 25, Suppl. A, 39-47, a copy of which is attached as Exhibit A). Azithromycin differs structurally from erythromycin by having a 15-membered ring rather than a 14-membered ring. Further, azithromycin lacks the C-9 ketone of erythromycin, having instead a (methyl)amino methylene group between the C-8 and C-10 carbons. As a result of its unique chemical structure, azithromycin has an exceptionally long elimination half-life (69 hours in humans), which permits successful therapy with once-daily dosing for one to five days. By contrast, erythromycin has an approximately two hour elimination half-life in humans, and must be dosed multiple times per day for many days. These elimination half-life distinctions reflect different sensitivities to metabolic enzymes in the human body, and are also reflective of differences in the chemical labilities of these two distinct antibiotics.

Clearly the declaration demonstrates numerous and significant differences between azithromycin and erythromycin, and in doing so demonstrates that no quick and easy conclusions can be drawn about azithromycin from what is known about erythromycin. The two drugs are simply too dissimilar in their behavior and their properties to make any simple, automatic conclusions. For this reason it is respectfully

submitted that it is untenable to combine Urquhart with Curatolo, in addition to which the two are directed to cross purposes - - controlled release versus immediate/fast release.

The rejection is based on hindsight

The invention relates to controlled release dosage forms of azithromycin, which dosage forms have an improved side effect profile. The scientific determination that underlies the invention is disclosed in the specification at page 6, lines 14-28:

The inventors conducted a series of studies in man in which the incidence and severity of gastrointestinal side effects were assessed after dosing azithromycin intravenously, orally, duodenally (via nasoenteric intubation), and ileally (via nasoenteric intubation). The studies demonstrated that the incidence of gastrointestinal side effects is relatively low after intravenous dosing, even at doses which are equivalent to a 5.4 g oral dose. Thus, while not wishing to be limited by or to any particular theory or mechanism, the gastrointestinal side effects of orally dosed azithromycin appear to be mediated by local interactions between azithromycin and the intestinal wall. Furthermore, the nasoenteric intubation studies demonstrated that duodenal azithromycin dosing results in more severe gastrointestinal side effects than does ileal dosing. The inventors accordingly determined that dosing azithromycin in a manner which reduces exposure of the duodenum to high concentrations of the drug results in decreased gastrointestinal side effects.

As explained above, the inventors based the invention on their determination that azithromycin side effects are mediated locally, in the upper gastrointestinal (GI) tract. It was this determination that formed the basis by which the inventors solved the problem of azithromycin side effects by formulating azithromycin in a controlled release dosage form that either reduces exposure of the upper GI tract to azithromycin or avoids such exposure altogether. Prior to the clinical studies, there was no reason to formulate azithromycin in a controlled release dosage form, particularly when considering that azithromycin has a long half-life. That is, azithromycin has a long half-life of 69 hours, meaning it takes 69 hours to purge half of the azithromycin administered in a previous dose. 69 hours is a very long time relative to the 6 hour time scale described in the application (see, for example, column 2, lines 13-31). Thus, in relation to the patentability of the instant invention, there is a fundamental issue for consideration: - - What would one of ordinary skill in the art possibly have hoped to accomplish by putting azithromycin in a dosage form that operates on a scale of several hours when azithromycin stays in the body for much, much longer, (one half still being present after a time on the order of 70 hours), in the first place? Only Applicants, by reason of the study

they disclose in their specification (and as quoted above) had motivation to formulate azithromycin in a controlled release dosage form.

Thus, prior to the inventors' clinical investigational work, there existed no basis on which to predict (1) whether GI side effects of azithromycin were mediated systemically or locally in the GI tract, or both; (2) that there even existed more sensitive and less sensitive regions of the GI tract; or (3) that sustained or delayed release dosage forms could improve the GI toleration of azithromycin.

From a somewhat different perspective, the Examiner stated, as an underpinninmg for the rejection, that

Urquhart et al. ... Column 1, lines 38-41 teaches drugs where administration to the stomach should be avoided, in line 40 is disclosed antibiotics such as erythromycin. [Office Action, Page 4, lines 5-7]

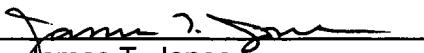
But, prior to the clinical studies described in the application, and as discussed above, it was not known that azithromycin side effects were locally mediated. Further, azithromycin is a different and distinct drug from erythromycin, and the Examiner has provided no basis supporting that conclusions about one may be applied to the other. The only basis for doing that is Applicants' own specification, and it is Applicants' position that that constitutes an impermissible application of hindsight.

To summarize, a rejection over the cited references is not tenable because their teachings are opposed. It is not tenable to combine references that teach away from each other. It is not tenable to base a rejection of an azithromycin delayed release dosage form on references that, in part, include teachings of immediate/ fast release as in Curatolo. The fact that Urquhart discloses that his invention is applicable to erythromycin has no bearing on Applicants' invention relating to a distinct and different drug.

In view of the foregoing comments and amendments, this case is believed to be in condition for allowance, and a Notice of Allowance is courteously solicited.

Respectfully submitted,

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